grammatically correct." Furthermore, the Examiner stated that "claims 11, 12 and 15 still contain improper Markush members... are so lengthy... and it is not easy to follow with all the additions and numerous deletions." The Examiner also stated that a clean copy of the pending claims "has not been submitted."

For the convenient reference of the Examiner, Applicant herewith submits a clean copy of the claims as they existed subsequent to entry of the amendments submitted on January 22, 2001. This clean copy should make it easier for the Examiner to follow the amendments submitted on January 22, 2001.

In response to the Examiner's § 112 rejections, Applicant has amended claim 5 to recite *"the preparation permeates through..."*, thereby correcting the grammatical error therein. In addition, Applicant has amended claims 6 and 9 to correct grammatical errors discovered by Applicant.

Applicant has also amended claims 11, 12 and 15 to refine the Markush groupings by removing alternative language and alternative terms. It is respectfully submitted that the Markush group in each of amended claims 11, 12, and 15, although lengthy, more particularly points out and distinctly claims the subject matter of the invention. Applicant respectfully points out that the length of a claim should not be the basis for rejection, if the claim is otherwise clear. Furthermore, it is respectfully submitted that there is no per se rule of indefiniteness concerning overlapping members where alternatives are recited in a claim (see: MPEP § 2173.05(o)). Accordingly, the Examiners's rejections should be withdrawn.

Rejection Under 35 U.S.C. §102

In the Office Action, claims 1 and 3-52 were rejected under 35 U.S.C. § 102(b) as being anticipated by EP 0220 797 (or Roberts US 4,921,706), Mayer (BBA, 1986), Blume (J. of Liposome Research, 1992), EP 0 707 847 (Bayer) or EP 0 704 206 (Regenold). The Examiner stated that EP 797 "discloses liposomes containing a drug, an amphiphilic lipid and a surfactant

in instant amounts and a method of preparation." The Examiner further stated that Roberts, Mayer, EP 847 and EP 206 similarly "all teach liposomes containing an amphiphilic lipid and a method of preparation" and stated that Blume and EP 160[1] "teach transfersomes and a method of preparation."

In response, Applicant respectfully submits that the claims of the present invention recite transfersomes, which are suspended in a pharmaceutically acceptable medium for application onto the skin or mucous membrane of a mammal, wherein the transfersomes comprise liquid droplets encompassed within a sheath comprising at least two amphiphilic liquid components which differ in their solubility in the pharmaceutical acceptable medium by a factor of at least 10, the two amphiphilic compounds being selected such that the transfersomes are capable of undergoing sufficient deformation to pass through the skin or mucous membrane without being solubilized.

By contrast, none of the cited references discloses transfersomes which undergo sufficient deformation to transport through skin or mucous membranes due to the selection of at least two amphiphilic lipid components which differ in their solubility in the transfersome medium by a factor of at least 10, such that the transfersomes undergo sufficient deformation to transport through skin or mucous membranes without being solubilized. Further, none of the cited references discloses that choosing two transfersome components can be manipulated in the manner claimed, e.g., in method claims 22-33, in order to obtain transfersomes which undergo sufficient deformation to transport through skin or mucous membranes. In fact, the Examiner apparently concedes that EP '847, EP '797, EP '206, the '706 patent, and Mayer are directed to liposomes containing only a single amphiphilic lipid, not at least two amphiphilic lipids as required by the claims of the present invention.

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[1] It is not clear whether the Examiner is relying on this reference, EP 0475160 (of record), since that reference had not been listed by the Examiner as a basis for the rejection. In any event, any reliance on EP 160 is respectfully traversed for the same reasons stated with respect to the Blume reference.

In particular, the liposomes of the EP '797 reference will not act in accordance with the transfersomes of the present invention. The liposomes exemplified in the EP '797 reference include stabilizers, which tend to strengthen the liposomes, or reduce their deformability.

In this regard, a Declaration[2] of the inventor, Professor Gregor Cevc, is enclosed herewith, which distinguishes the invention from the cited prior art. This Declaration demonstrates that liposomes made in accordance with the EP '797 reference (e.g., Example 1) are not able to pass through a filter (an Anapore membrane with 20 mm pores). Although Example C of the submitted declaration is not specifically exemplified in the present invention, Applicant respectfully submits that a comparison of the examples of the '797 reference with the examples of the present invention will provide for the same results.

Furthermore, the Examiner stated that "the methodology used in the preparation of instant compositions is the same as the classical method of preparation of liposomes using one or more amphiphatic lipids."

In response, Applicant respectfully submits that, although manufacturing techniques for liposomes may be suitable for the manufacture of transfersomes, the transfersomes of the present invention differ from liposomes for the following reasons: i) transfersomes are much larger than conventional Micelle-like carrier formulations and are subject to different diffusion laws, for example, transfersomes permeability is not a linear function of the driving pressure, as it is in the case of liposomes. In the case of transfersomes, the permeability increases disproportionately or nonlinearly as the pressure increases (see: specification page 5, first paragraph); ii) substances introduced through constrictions by means of transfersomes, can develop in man almost 100% of the maximum obtainable biological or therapeutic potential (see: specification page 5, first paragraph); iii) the transfersomes either do not have a solubilization point or are far removed from the solubilization point and permit the rapid and effective transport of active ingredients

[2] This Declaration of Gregor Cevc was originally submitted during the prosecution of a related U.S. case (U.S. Patent Application Serial No. 07/844,664, now U.S. Patent No. 6,165,500).

through barriers and constrictions (see: specification page 6, first paragraph).

Accordingly, it is respectfully submitted that the rejections under 35 USC § 102 have been obviated and should be removed.

Rejection Under 35 U.S.C. § 103

In the Office Action the Examiner rejected claims 1 and 3-52 under 35 U.S.C. § 103(a) on the grounds of being unpatentable over the references cited above with respect to the § 102 rejections. The Examiner stated that, although "the references teach liposomes or transfersomes containing a drug an amphiphilic lipid and a surfactant in instant amounts and a method of preparation", "[i]t is unclear whether the references teach all of the instant functional parameters. In case they are different, in the absence of showing the criticality, they are deemed to be parameters manipulated by an artisan to obtain the best possible results."

Applicant respectfully traverses this rejection. Contrary to that stated by the Examiner, it is very clear none of the cited references discloses transfersomes which undergo sufficient deformation to transport through skin or mucous membranes due to the selection of at least two amphiphilic lipid components that differ in their solubility in the transfersome medium by a factor of at least 10. Furthermore, none of these references teaches or discloses transfersomes that undergo sufficient deformation to transport through skin or mucous membranes without being solubilized.

Further, none of the cited references hint or suggest that choosing two transfersome components can be manipulated in the manner claimed, e.g., in method claims 22-33, in order to obtain transfersomes which undergo sufficient deformation to transport through skin or mucous membranes. In fact, the Examiner apparently concedes that EP '847 EP '797, EP '206, the '706 patent, and Mayer are directed to liposomes containing only a single amphiphilic lipid, and these references contain no suggestion for the liposomes to contain two or more amphiphilic lipids.

The Examiner takes the position that, absent a showing of criticality, these parameters would be manipulable by one skilled in the art in order to arrive at the present invention. However, regarding the manipulability of the parameters, Applicant respectfully submits that the Examiner has failed to provide evidence to support his position. The Examiner has not introduced any reference which teaches that, for example, one can select at least two components that differ in their solubility in the transfersome medium by a factor of at least 10, in order to provide transfersomes which undergo sufficient deformation to transport through skin or mucous membranes. Absent such, the Examiner's rejection cannot stand.

With respect to the Examiner's position concerning the absence of criticality, it is respectfully submitted that the specification of the present invention **provides ample evidence** that the preparations of the prior art do not perform (i.e., their permeation capability is significantly less than that of) the claimed invention. On page 31, lines 10 and 11, pages 40-41 and in Figures 3 and 8 of the subject application, Applicant has shown that the permeation capability of liposomes (including the liposomes of EP '797) is lower than that of Applicant's transfersomes.

In this regard, the Examiner's attention is respectfully directed to page 32 of the specification, wherein the carrier permeation capability of Examples 5-6 is compared to prior art liposome preparations. It is stated therein, and shown in Figure 4 of the specification, that the transfersomes of the subject invention formed from SPC and didecanoyl phosphatidyl choline have a higher permeation capability than do the liposomes formed from pure SPC.

Further, included in the specification at pages 38-41 are Comparison Examples A to E which are directed to formulations described in the prior art. Comparison Example D is actually Example 4 of EP 0220 797, relied upon by the Examiner (see page 40 of the specification). At page 41 of the specification, Applicant stated:

> In Figure 8, the permeation capability (at a constant pressure of 0.9 MPa) is shown for the Comparison Examples A to E and for an inventive ibuprofen/SPS

> transfersome in the form of a bar graph. It is clearly evident from the bar graph (Figure 8) that, at an elevated pressure (0.9 MPa), the permeation capability of the compositions of the Comparison Examples A to E ***is significantly less than that of the inventive transfersomes.***

(Emphasis added). Therefore, Applicant has already demonstrated the advantageous results obtained by the claimed preparations and methods, contrary to the Examiner's assertion.

Accordingly, Applicant respectfully submits that the rejections under 35 U.S.C. §103 have been obviated and should be removed.

Conclusion

It is respectfully submitted that the rejections in the Office Action have been obviated and should be withdrawn. Applicant respectfully submits that the pending claims are now in condition for allowance. Should there be any outstanding issues remaining, the Examiner is urged to contact Applicant's attorneys.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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Version Of Claim Amendments With Markings To Show Changes Made

5. (Twice Amended) The preparation of claim 1, wherein the preparation permeates through said skin or mucous membrane at least 0.001% of the permeability of small molecules, which permeate essentially without being impeded.

6. (Twice Amended) The preparation of claim 1, wherein the permeation capability relative to reference particles $P_{(transfer.)}/P_{(refer.)}$, the reference particles being water, is between 10^{-5} and 1.

11. (Twice Amended) The preparation of 1 , wherein at least one amphiphilic lipid component is selected from the group consisting of a diacyl or a dialkyl glycerophosphoethanolamino azo polyoxyethylene derivative, a didecanoyl phosphatidyl choline, a diacyl phosphooligomaltobionamide, a glyceride, a glycerophospholipid, a isoprenoid lipid, a sphingolipid, a steroid, a sterol, a sulfur-containing or a hydrocarbon-containing lipid [or a different lipid, which forms stable structures, such as double layers], a half protonated liquid fatty acid, a phosphatidyl choline, a phosphatidyl ethanolamine, a phosphatidyl glycerol, a phosphatidyl inosital, a phosphatid acid, a phosphatidyl serine, a sphingomylein or a sphingophospholipid, glycosphingolipid, a cerebroside, a ceramide polyhexoside, a sulfatide, a sphingoplasmalogen a ganglioside [or other], a glycolipid, [or], a synthetic lipid, a dioleoyl, a dilinolyl, a dilinolenyl, a dilinoloyl, a dilinolinoyl or a diarachinoyl, a dilauroyl, a dimyristoyl, a dilalmitoyl, a distearoyl phospholipid [or] a corresponding dialkyl, [or] a sphingosin derivative, and a glycolipid [or other identical chain or a mixed chain acyl lipid and an alkyl lipid].

12. (Twice Amended) The preparation of claim 1, wherein the less soluble amphiphilic lipid component is selected from the group consisting of a myristoleoyl, a palmitoleoyl, a petroselinyl, a petroselaidyl, a oleoyl, elaidyl, a cis- or trans- vaccenoyl, a linolyl, a

linolenyl, a linolaidyl, a octadecatetraenoyl, a gondoyl, a eicosaenoyl, a eicosadienoyl, a eicosatrienoyl, a arachidoyl, a cis- or trans-docosaenoyl, a docosadienoyl, a docosatrienoyl, a docosatetraenoyl, a caproyl, a lauroyl, a tridecanoyl, a myristoyl, a pentadecanoyl, a palmitoyl, a heptadecanoyl, a stearoyl or a nonadecanoyl, a glycero-phospholipid [or a corresponding chain-branched derivative or a corresponding sphingosin derivative], a glycolipid [or], an acyl lipid [or a] and an alkyl lipid [; and the more soluble component or components derived from one of the less soluble components derivatized with a butanoyl, a pentanoyl, a hexanoyl, a heptanoyl, a octanoyl, a nonanoyl, a decanoyl, a dodecane, a undecanoyl, a monosaturated substituent thereof, a polyunsaturated substituent thereof and a chain-branched substituent thereof].

15. (Twice Amended) The preparation of claim 1, wherein the active ingredient is selected from the group consisting of an adrenocorticostatic agent, a β-adrenolytic agent, an androgen or antiandrogen, an anti-parasitic, an anabolic, an anesthetic or an analgesic, an analeptic, an anti-allergic, an anti-arrhythmic, an anti-arteriosclerosis, an anti-asthmatic [or], a bronchospasmolytic agent, an antibiotic, an anti-depressive [or], an anti-psychotic agent, an anti-diabetic agent, an antidote, an anti-emetic, an anti-epileptic, an anti-fibrinolytic, an anti-convulsive [or], an anti-cholinergic agent, an enzyme, a coenzyme, a corresponding coenzyme inhibitor, an antihistamine, an antihypertensive drug, a biological activity inhibitor, an antihypotensive agent, an anticoagulant, an anti-mycotic, an antimyasthenic agent, an active ingredient against Parkinson's or Alzheimer's disease, an anti-phlogistic, a anti-pyretic or an anti-rheumatic agent, an antiseptic, a respiratory analeptic [or], a stimulating agent, a broncholytic, a cardiotonic [or], a chemotherapeutic agent, a coronary dilator, a cytostatic agent, a diuretic, a ganglion blocker, a glucorcorticoid, a therapeutic agent for influenza, a hemostatic agent, a hyptonic agent, an immunoglobulin [or], a fragment or a different immunological [or], a receptor substance, a bioactive carbohydrate, a bioactive carbohydrate derivative, a contraceptive, a migraine agent, a mineral corticoid, a morphine antagonist, a muscle relaxant, a narcotic, a neural therapeutic agent [or], a CNS therapeutic agent, a nucleotide [or], a polynucleotide, a

neuroleptic agent, a neuron transmitter, a neuron transmitter antagonist, a peptide, a peptide derivative , an ophthalmic agent, a para-sympathicomimetic or para-sympathicolytic agent, a protein, a protein derivative, a psoriasis/neurodermatitis agent, a mydriatic agent, a mood elevator, a rhinological agent, a sleeping draft [or], a sleeping draft antagonist, a sedative, a spasmolytic, a tuberculosis agent [or], a urological agent, a vasoconstrictor [or], a vasodilator, a virostatic agent [or], a wound-healing agent, diclofenac and ibuprofen.